KEYNOTE ADDRESS:
HIV AND LABORATORY SCIENCE

Wanda K. Jones, Dr.P.H.
Department of Health and Human Services, Washington DC
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I would like to look at where we have been in the HIV testing and policy arena, and open up some issues I think might be on the horizon. I will not be focusing much on blood banks. I also want to remind you of where we are in this epidemic, and how we might expect it to evolve. Remember, I am not a fortune teller and I cannot predict the future, and I do not pretend to be an expert on any of this, but I am a willing provocateur. I recognize many of you were there from day one, and though you were witness to the same events, you may have entirely different perspectives and views of how things played out. There should be time at the end of my remarks for questions and comments, so maybe we can have some fun.

The bottom line is that medicine is coming home. Home testing for any of a number of maladies either is already available or soon will be, giving new meaning to the term "sink testing", and HIV testing is not exempt from this trend. How have we come this far? We are nearly twenty years into this epidemic. It is an anniversary we will be observing shortly after the millennium. In the early days we did not know quite what we were dealing with, but a virus very rapidly became suspect. We were not sure about how this organism was being transmitted. We looked at who was sick and what they did, and concluded that sex, drugs, and blood products were very risky. We crafted messages about avoiding sex and drugs, but we could not be completely frank. We had great difficulty going beyond a mainstream message for a variety of reasons. A number of surrogate tests, markers of high risk behaviors, were identified to start protecting the blood supply. None of this was good enough because we had no way of testing for a virus we had not yet found. Too many women, men, and children paid with their lives.

By 1985, we had found the virus and developed a licensed antibody test to be used in blood banks. But we did not want to attract high risk people to blood banks, so we set up counseling at testing sites to accommodate demand. We still did not know much about the natural history of HIV disease and AIDS, and fear gripped much of the nation. In the laboratory, we were wrestling with complex algorithms to ensure we were not wrong. We took our time with the tests, counseling people about risk behaviors and the meaning of test results both before and after testing. The price of error was truly staggering. People with AIDS became twentieth century lepers, banished from their jobs, homes, families, and communities. ‘Denial’ is more than a river in Egypt, and there was no way this nation could accept the fact that this virus could affect us. It only happens to ‘them’, and of course, to the poor, to innocent babies, to people with hemophilia, and to healthcare workers. For a generation too young to remember polio, the generation that drove the sexual revolution and benefitted from the civil rights movement, HIV/AIDS was a wake up call that we dare not squander our inheritance.

Around every corner between 1985 and 1990, was a new test promising more sensitivity or specificity in detecting antibody. We had micro titer and bead-based ELISAs. We had whole virus lysates, spiked protein, and synthetic recombinant formats. In a very short time we

moved from relatively crude handheld washing and dispensing devices that were the bane of standardizing technique and doing large numbers of tests, to fully automated instruments that took a tube of blood and yielded an answer. But these tests, with their near 100 percent sensitivity and specificity, still were not good enough to report a result. Anything that screened positive with these assays was sent for confirmatory or supplemental testing by Western blot or immunofluorescent assay (IFA). The original Western blot and IFA's were homemade, but finally commercial companies were able to secure approval from FDA, and then the real debates began.

Among the Western blots some products showed more bands than others. Among the IFA's, staining patterns and colors varied with cell lines and reagents. It was here that the Association of State and Territorial Public Health Laboratory Directors, now known as the Association of Public Health Laboratories (APHL) stepped into the breach. Bill Hausler, Joe Joseph, and Art DeSalvo were leaders in recognizing the need for a unified approach to testing, and particularly to reporting results. Their aggressive pursuit of this goal was exactly what we needed. The partnership of CDC and FDA with APHL, and the involvement of commercial companies in that process created a powerful and groundbreaking alliance that has been grossly undervalued for the difference it made in assuring that HIV test results were as near perfect as any human run testing system could be. It serves as a model even today for the way in which we should approach new technologies in any number of fields.

When the first consensus conference was held in May of 1986 in Kansas City only the Abbott ELISA had been approved by FDA. But by the time of the third conference, there were at least a dozen different EIA's, Western blots, and IFA's approved for either screening or confirmatory testing. Those first consensus conferences were exciting and sometimes painful meetings for laboratorians who were new to standard- setting debates. Agreeing on screening and confirmatory algorithms, debating which Western blot bands were most important, and defining appropriate quality assurance and performance evaluation were laborious and intense processes that were revisited annually as the technology and data evolved.

In 1987, we undertook dried blood spot analysis. In 1989, CD4 tests and direct detection by molecular biologic assays entered the fray. We became even more conscious of the social debate that whirled right outside of our doorway and outside our meetings. As new evidence about the efficacy of treatment came spilling out, the demands for faster testing, more appropriate counseling, and earlier detection mounted, and we could not continue to ignore it in the HIV testing arena. We had worked through the scientific issues of laboratory testing such that, barring specimen mixup, anyone could be assured that reputable laboratories were reporting reliable results on screening tests and on tests to monitor HIV progression. This is truly the finest legacy of the APHL, CDC, and FDA partnership. But even more contentious debates were brewing. Growing evidence for the validity of testing specimens other than blood using modified assays increased the demand to do so, and the possibility of doing rapid tests in the United States also arose.

With a still mounting epidemic, it was clear we were not reaching all those who could benefit from early treatment because they did not know their HIV status. These individuals continued to infect others. With the routine two week waiting period between testing and results at many public clinics, some 60% of those tested never returned for their results. If clients' results were positive and their identity was known, health departments tried to find them to encourage them to be seen for treatment and

follow-up. However, some of us saw this as a terribly inefficient way of doing business. Clearly, something in the system was broken. The history of that two week wait is mired in complex, technical, policy, operational, and moral issues. Early on, testing was fairly centralized because of complexity and cost, and most specimens were sent out. The accepted algorithm of screen and re-screen in duplicate followed by confirmatory testing took 2-3 days, at a minimum, in even the most efficient laboratories. Many public health departments were further hampered by shortages in staff and funding. Clients needing services were placed on waiting lists. The two week interval between specimen collection and result reporting to the client became the norm. For some, the two weeks was an opportunity for moral suasion. The promiscuous could mend their ways, the drug user could come clean. All the risky behavior identified or alluded to in the pretest counseling would be re-examined by the worried test taker, and a booster shot of post test counseling would effect change.

If nothing else, this epidemic has taught us how little we know about human behavior. With so many people lost to follow-up, it was time to re-examine the available technology, and revisit the approach to testing. From a cost standpoint alone, the fact that over 60% of the testing and pre-test counseling efforts were essentially discarded was nonsensical. International AIDS efforts have long shown the efficacy of algorithms using rapid simple tests. However, only two, the latex agglutination assay of Cambridge and the Murex SUDS, have been approved for use in the United States, and for very limited use. A few of us at CDC and elsewhere began to discuss assessing the utility of rapid tests. Thanks to Mary Guinan, I finally made contact with David Holtgrave, Paul Farnham, and the late Robin Gorsky, and we began to look at this issue systematically. My colleagues were not laboratorians, so they saw testing algorithms from a different perspective. We chose a reasonable model and tested it against several price, prevalence, acceptance, and predictive value factors and compared it with the standard approach. We demonstrated potentially significant economies, at least in theory. Bill Kassler heard about our work and wanted to test a similar model in a health department. What was obvious to all of us was that the counseling message and structure had to change if we were to succeed. We worked hard to define and test what that message and structure would be.

In March of 1993 at the 8th Annual Conference in Atlanta, I suggested it was time to consider when it would be appropriate to give a provisional result which was highly likely to be true if positive. I likened this to messages people have heard for years about other serious disease possibilities: Patients are told over the phone, sometimes via answering machine or voice mail, that their tests were suspicious or unexpected and they should come back in to see the doctor as soon as possible. We were not proposing to give HIV results over the phone, or by letter, or via answering machine. We were proposing the client simply get their results in the same clinic visit. It was immediately obvious that some did not like this proposal. Nonetheless we developed a protocol, and worked with Dallas County Health Department in Texas to test the proposed model. The end result was that it was a success in terms of economy, clinic efficiency, and client acceptance. It was not perfect, but it was a start and yielded data that showed us we could begin to look at this issue. It brought us to a novel concept: testing and counseling that could actually meet client needs.

I began promoting the idea that we re-visit our approach to testing through a variety of means. Although I had little data, I focused on the broader issues of policy and outcome. I met a lot of resistance at the STD meeting in Atlanta and at the Retrovirus Testing Conference in Reno in 1994. However, in the arena of meet-

ing client needs it was clear that one possibility whose time had come was the home collection kit. It was first introduced in 1987 primarily to address the concerns of stigma and adverse consequences if results became known or one were seen walking into a known HIV testing site. But the world was not ready in 1987, and there were plenty of technical reasons to send the kits back for refinement. Further, it was feared that people who got HIV test results over the phone would become suicidal, or sociopathic, or at the very least they would continue to infect others because they were unknown to us. It was conversely reasoned that people who got negative results would have their risky behaviors reinforced because they had been 'rewarded' for testing negative. This presumed we had some control over what people did when they left our clinics with their results. This argument stood as an obstacle for five years, as we in public health stood unified in our opposition to home collection. As the technical issues were overcome and a few small studies showed that telephone counseling did not lead to the feared reactionary behaviors, this argument began to crumble. The debate and speculation on all sides were absolutely rancorous. At one point I made the private statement that we would all prefer that the rapid tests not be licensed, in reference to the difficult issues that we were having great problems resolving. The statement was repeated inappropriately and caused some ill will, having been taken out of context. Yet this forced us to focus more clearly on our precise concerns and to try to identify ways in which the issues could be addressed and to work through those issues. Finally, the FDA approved two products, although today only one remains on the market. The first was withdrawn after only a few months, because of poor sales. And to my knowledge, there have been no reports of suicide or sociopathic behavior.

I cannot resist sharing just a couple more stories of intended and unintended consequences of technology. HIV had so aroused our suspicion of anomalous viral diseases that a number of maladies or syndromes came under study for possible retroviral origins. HTLV-1 had been known as a cause of T-cell leukemia in some parts of the world for many years. The similarities of that disease and what became to be known as AIDS led early investigators into retroviruses, and eventually to the discovery of HTLV-III by Luc Montagnier and Robert Gallo. Soon other clinical entities were worked up for retroviruses. One day we were called about a hand full of patients with depressed CD4 counts, but they were HIV and HTLV negative. We obtained sequence data thinking the entity may prove to be a new virus. The sequence we were sent matched a goat retrovirus, and we were perplexed. The investigator and CDC personnel went back to the lab with renewed vigor to try to figure this out. Within six weeks we had a public meeting on what came to be known as Idiopathic CD4 T-lymphocytopenia or ICL. In over two years of monitoring afterward, this remained a disease without a cause. No virus or reliable test was found. We learned from this experience and certainly from HIV that we did not serve anyone well by keeping something like this a secret. Others had seized upon it as the proof they needed that HIV was not the cause of AIDS, and for a number of years we spent a significant amount of time rebutting their arguments. This forced us to mention our rigor in laboratory and epidemiological investigations of HIV/AIDS. Today, that argument is much less salient.

I will share another story now, a sadder one for the telling. AZT has been shown to reduce the risk of perinatal HIV transmission by as much as two-thirds. When these results were about to be announced we were six years into the blinded testing of dried blood spots of newborns. In an internal meeting to discuss how we would respond to the pending announcement, I suggested that we look at this testing. Of

course, I knew the newborn was not the point of intervention. Of course, I knew the valuable information we gleaned from this effort. And, of course, I knew this surveillance system was our only means of evaluating the effectiveness of any effort at promoting counseling, testing, and AZT treatment of HIV infected pregnant women. But I also knew in my heart the public would not accept any of these facts, because they would not understand it. The public would not see the maternal intervention, only all those babies we were not saving, because we did not know who they were. I was the only person in the room to mention this, and I was not heard. At that point we were having to address demands for mandatory testing of pregnant women, when testing itself was not the intervention, treatment was. In order to facilitate adherence to a complex and lengthy treatment, we believed we needed to engage and support women, and mandatory testing was not the way to do that.

Well, you know the ending to this story, and I am no prouder of this ending than you are. The program may well have died anyway, but had we dealt with it constructively and proactively early enough, I think it could have been saved in some form. I know many bright, well intentioned people who know much more about the substantive issues than I do, disagree on this. But we really have no way of knowing how well voluntary counseling, testing, and AZT treatment for HIV infected pregnant women is working. In fact, even if we were under a testing mandate, we still would have no way of knowing how effective it was. For me, this experience brought home the fact that laboratory testing conducted for even the grandest of public health goals is not conducted in a vacuum. We must never forget that fact, and we must remain vigilant to not become the unintended victims of larger policy debates. For all our rigor and our vigor in ensuring the best testing, we can see it all evaporate if we are not at the table for that debate.

On the positive side, however, we have much to show for our rigor. Today, we have screening and confirmation available on oral mucosal transudate, and screening and confirmation available for urine. And while these tests follow the conventional EIA/ Western blot algorithm, they are being modified for faster turnaround and for possible home use. These tests created a bit of public confusion when they were first approved and announced. This is a public that is still somewhat convinced that you can get HIV any number of ways that the government is not disclosing. So the testing of oral transudate and urine appear to indicate to them that these are obviously also ways to spread HIV. We know this is not the case. I believe the laboratory community and other practitioners have done an excellent job trying to address these concerns, but we always have to remember the possible perceptions and misperceptions and the adverse effect they can have on our very best intentions and our very good work.

Today, we also have very sophisticated DNA technology that tells us not only what might have been the source of infection or the strain, but also helps us track the dramatic decrease in copy number with triple drug treatment, and rebounding numbers when resistance is encountered and treatment fails. We are using molecular technology to learn about the precise mechanisms the virus uses to establish infection both in terms of potential genetic risk and protective factors of the host, and in terms of the timing of viral specific gene expression which give us potential new targets for treatment. There is even renewed effort in vaccine development. It feels as though we could be close to a breakthrough with very exciting discussions and work underway targeting cellular and humoral immunity with vaccines. It really is quite a change from where we were five years ago in our activities with the working group on HIV vaccine development of the Federal Coordinating Counsel on Science, Engi-

neering, and Technology. But our efforts faded because it seemed we weren't going to see anything happen. This disease has given us a wild ride with promises of surrogate tests that would save the blood supply, Secretary Heckler's prediction of a vaccine in two years after the discovery of the virus was announced and first AZT and then triple drug therapy that prolonged disease free living, so that people with HIV could remain productive and active citizens.

HIV, like so many other infectious organisms, is dynamic and highly adaptive. While our hopes remain high for treatment, we are beginning to see those hopes crushed on the rocky shores of reality. A vaccine is our best hope if our history with other viruses and infectious organisims remain true. We have never eliminated any viral disease without a vaccine. Someday we will have one. It may not be perfect, but it wouldn't have to be if it reduced the risk of transmission, if we got enough people immunized, and if it ameliorated the course of infection. Liken it to the flu vaccine, as a worse case scenario, and you can see what an impact it would have globally. Of course, we will need sophisticated tests that can differentiate vaccinated persons from those who are truly infected, and even differentiate persons who have been vaccinated but who are also infected. I know work is underway in this arena, but I remind you again as laboratorians and as researchers, it has to proceed in parallel with vaccine development efforts in order to be useful.

Well, what will we face as we approach a successful vaccine? We know today that over 640,000 AIDS cases have been reported in the United States. Last year over 20% of AIDS cases were reported among women, and among HIV cases a large proportion were also among women. I predict we will actually see that proportion hit 50% before we have a vaccine. And we in the United States will then match the global picture. We have not done a good job in prevention strategies for women. Too often women are not aware of their partner's risk for HIV. Maybe they don't ask, or maybe they're lied to. Maybe they don't ask because they are afraid of a violent reaction, or of being left alone, or of not getting the drugs, or diapers, or food, or shelter that they are promised in exchange for sex. Or maybe they still don't know they should ask. "Use a condom" we say, but who really controls that? We know there are ways a condom can be worked into foreplay, but basically this is about power in relationships, and too few women at risk have the power to protect themselves. "Use the female condom" we say. This requires cooperation, and it is not exactly a stealthy device. I cannot tell you how many women have told me how their partner removed it or purposely bypassed it. Spermicides have not been shown to be effective in reducing the risk of HIV transmission, but have provided some protection from STDs. Although spermicides may be better than nothing, we cannot risk over-selling them if they may actually prove to do more harm than good. Only life long abstinence is 100 percent effective in avoiding any sexually transmitted disease. But, that strategy applies to less than 1% of our adult population. Therefore, more women will become infected before we have a vaccine.

Testing modalities will likely change as well. Rapid test algorithms will become more commonplace as tests are approved, and I believe they will not include a confirmatory test as we now define it. In fact, testing of blood, except in the blood bank, will likely become a rare event particularly for screening people at risk. I also believe home tests will become available, although not immediately.

Assays currently in development to rapidly screen for antiviral resistance will become commercially available, and these will become part of the routine monitoring of the infected

patient. We will detect the virus earlier, conceivably within hours or days of infection, and prophylaxis will become commonplace. What we have nearly succeeded in doing is transforming HIV disease into a chronic disease model. And as with many chronic diseases, I believe we will see significant home monitoring done by patients. Technology is evolving so rapidly, it is conceivable that viral load, CD4+ counts, drug levels, and other T-cell assays will be done with handheld devices similar to the I-stat, or on color developing cards or strips similar to glucose monitors using blood or perhaps urine or other body fluids, or perhaps even transdermal monitoring of some analytes. Another possibility is a skin patch or a pincher-like device connected to an arm or a leg, which can be connected to a phone line with encrypted signal transmitted over a digital satellite network to a central laboratory or health care provider. These technologies are all being currently researched for various purposes. Some of them have not moved toward the HIV testing area yet, but they are certainly being explored in other areas and it truly is just a matter of time.

We are living in an exciting time and we will see changes like these in our lifetimes. We can be proud of the massive change that HIV has driven even as we are humbled by the destruction it has wrought. We can be proud of what HIV has taught us in the laboratory, and how we have applied those lessons to newer diagnostic challenges like Lyme disease, hantavirus, and hepatitis C. We can be proud that we have stood together to do the right things for the right reasons at the right times. We should not fear change. We should prepare for it and embrace it, for it is the only thing that is constant. We must never forget that this virus has killed almost 400,000 men, women, and children in this country, and millions more worldwide. It will kill many more before we can turn off the lights and go home knowing that we have finally wiped it off the face of the earth. Thank you.